Pulmonary thromboembolism

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Pulmonary thromboembolism (PTE)

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Definitions

Thrombosis is the local formation of a thrombus inside a vessel leading to vascular occlusion, embolism is the vascular occlusion by various formations like a thrombus, tissue particle, parasite, foreign body, tumor cells or air that have been formed distant to the actual occlusion and that are carried in the vessel to the site of occlusion, and thromboembolism is thus the vascular occlusion specifically by a thrombus that was not produced at the site of occlusion but carried there. Once a thrombus is present in the circulation it may grow. In this text, the abbreviation PTE will be used to describe both pulmonary artery thrombosis and / or embolism and / or thromboembolism.

Pathogenesis

For PTE to occur, an important disturbance in the very delicate balance between pro- and antithrombotic body systems has to be present, i.e. there may be excessive abnormal focal vascular triggers of coagulation, a systemic hypercoagulable state, or a systemic hypofibrinolytic state.

Diagnosis

Pulmonary thromboembolism (PTE) in dogs is probably underdiagnosed. Its presence may be suspected in patients with documented hypoxemia or hypercarbia, affected with a disease with known risk for PTE, coagulation abnormalities, suspicious radiographic findings, and the echocardiographic recognition of pulmonary hypertension (PH). Depending on the severity of PTE however, arterial oxygen content, routine coagulation parameters (PT, PTT, TT), thoracic radiographs and echocardiography may be unremarkable.

Likewise, the clinical abnormalities are quite variable and may range from asymptomatic to mild cough, exercise intolerance, right sided heart failure, severe dyspnea to quite unexpected death. The clinical abnormalities depend on the underlying cause as well as on the extent of the thrombosis.

Not only severe and symptomatic PTE is a life threatening condition, but also mild and subclinical PTE is dangerous, because it may progress to severe PTE.

Probably the most important diagnostic clue to detect PTE is a high index of suspicion. Important diseases with known risk for PTE include

- autoimmune hemolytic anemia
- hyperadrenocorticism
- nephrotic syndrome
- severe pancreatitis
- septicemia
- cancer
- pulmonary artery parasites and vasculitis (*Dirofilaria immitis, Angiostrongylus vasorum*)

Thus, if one of these diseases is known to be present, also PTE must be considered to be present or to develop, and dogs affected with one of these conditions have to be closely monitored for signs suspicious for PTE.

Experimental findings on test performance in PTE

Angiostrongylus (A.) vasorum infection in experimentally infected dogs consistently causes pulmonary artery lesions with PTE at the time of patency, and in naturally infected dogs has been shown to sometimes cause severe PH. Experimental infection of *A. vasorum* allows to study the effects of PTE on various above mentioned parameters in a well defined system. Some of the findings shall be described below.

In one study, 3 healthy Beagles were experimentally infected with 50 and 3 with 500 larvae. Clinical and fecal Baermann examinations were done daily. Thoracic radiographs and femoral arterial blood gas analyses were performed 8 and 13 weeks (w) post infection (pi), and 9w post therapy (pt). Echocardiography was done at time 0 and 2, 5, 8, 13wpi, and 9 wpt. Invasive pulmonary artery pressure (PAP) measurements under sedation were obtained 8 wpi. Four dogs were treated with a parasiticide at 13 wpi. The prepatent period lasted 47-49 days, and around the same time (42-56 days pi) the first respiratory signs were observed. Radiographic abnormalities were marked at 8 wpi with obvious progression to 13 wpi; besides pulmonary parenchymal lesions, several dogs developed pleural effusion. The pulmonary lesions were paralleled by moderate hypoxemia with a median PO_2 of 73 and 74 mmHg at 8 and 13 w pi, respectively. No 2D, M-Mode or Doppler echocardiographic changes including Tei-index were observed at 2, 5, 8 and 13 w pi. No relevant PH was discernible at any time; median calculated RV-RA-gradients were 24 mmHg at time 0, and ranged between 19

and 24 mmHg at the different time points pi and pt. Invasive PAP measurements at 8wpi revealed median sPAP and dPAP of 31 and 15 mmHg, respectively. Radiographic lung changes and blood gas abnormalities correlated with clinical signs, but not with echocardiographic findings. Four of the 6 dogs were treated, and 9 wpi the radiographic abnormalities had mostly resolved, leaving only a mild interstitital pattern. Upon necropsy in 2 untreated dogs (infected with 50 and 500 larvae) subjectively the lungs were similarly affected and estimated to be around 80% abnormal. Histological lesions included severe inflammation, hemorrhage and thrombosis. In the four treated dogs, there was still evidence of thrombosis at the time of necropsy, 9wpt. The mentioned interstitial pattern on radiographs in these was due to fibrosis. In this study, marked pulmonary changes in *A. vasorum* infection were not associated with abnormalities in cardiac function using conventional routine echogcardiograpy and did not cause measurable PH. It was concluded that relevant PH may only develop at the time of acute and more severe pulmonary thrombosis. It was further speculated that newer ultrasound techniques might be more sensitive to detect changes in right ventricular function in face of marked pulmonary disease.

The same 6 dogs were also examined by computed tomography to characterize the pulmonary lesions more exactly than with routine radiographs. Contrast CT was expected to help identifying arterial thrombosis. A first CT was done 13 weeks post infection (wpi) in all, and a second 9 weeks after treatment (wpt) in 4 dogs. CareDose was used to choose mA automatically as low as possible. Scanning parameters were 120 kV and a pitch of 1.2. Rotation time was 1 second. The images were reconstructed in 1.5 mm slices. The post contrast scan was done 20 seconds after administration of Telebrix®35 (2.5ml/s, 2 ml/kg BW). At 13 wpi, severe consolidations with airbronchograms, large nodules and extensive areas of ground glass opacifications were found in the periphery of all lung lobes. Bronchi and lymph nodes were normal. Mild pleural effusion was found in five dogs. Post contrast CT revealed abruptly stopping vessels. At 9 wpt the consolidations, large nodules, pleural effusion and vascular abnormalities had resolved. Mild interstitial opacifications, subpleural interstitial thickening, subpleural lines and interface signs could still be observed, independent of the severity of the infection. In the very periphery of the airways slight bronchial dilatation could now be identified. Expectedly, CT allowed a much better and more exact judgment of lesion distribution and severity. However, for detection of PTE the

CT results were disappointing. For one thing, the image quality using CareDose was not considered optimal and post contrast CT does not fulfill the requirements for angio CT.

In a second study the focus was put on newer echocardiographic modalities, i.e. Tissue Doppler Imaging (TDI) and contrast echo. An additional goal was to document arterio-venous shunting during experimental infection and during therapy. It was further hypothesized that PH may develop right at the time of treatment, when many worms die. In this study, six healthy Beagles were infected with 200 L_3 larvae. TDI (pulsed wave, RV longitudinal myocardial velocity basal segment), contrast echo with agitated saline and pulmonary transit time with SonoVue^R, as well as invasive PAP measurement were performed pre infection (T0), once 7 to 12 weeks post infection (T1) and once during the first five days after parasiticide therapy (T2).

Tei and Tei_{TDI} indexes did not change over time. In the TDI variables analysed there was a decrease in peak myocardial velocity in systole (S_{TDI}) and an increase in time to peak systolic contraction (T_{peak}) with a median S_{TDI} of 0.130 m/s (0.123-0.194), 0.128 m/s (0.087-0.173) and 0.117 m/s (0.083-0.152), and a median T_{peak} of 0.097 ms (0.074-0.149), 0.109 ms (0.102-0.196) and 0.149 ms (0.104-0.234) at T0, T1, and T2, respectively. The E/A_{TDI} ratio decreased from T0 1.13 (0.94-1.55) to T2 0.91 (0.54-1.38). At T0 all dogs showed negative, and at T1 and T2 5 of 6 dogs showed positive contrast studies for shunts. Median pulmonary transit time was 4 beats respectively 2.3 seconds at T0 and no change was observed at T1 and T2. Invasively measured PAP slightly increased over time with median sPAP of 24, 25 and 29 mmHg and dPAP of 10, 11 and 18 mmHg, respectively. Two dogs showed mild PH at T2 (sPAP 33 and 30, and dPAP 20 and 25 mmHg); both had $E/A_{TDI} <1$.

In conclusion, in dogs with marked pulmonary vascular disease, associated PTE and mild increase in PAP, effects on RV function were detectable using TDI but not conventional echo.

In face of severe pulmonary disease the majority of dogs developed intrapulmonary arterio-venous shunts in the absence of relevant PH. Parasiticidal therapy did cause an increase in PAP, but not to a clinically relevant degree.

For most clinicians, plasma D-dimers have become an important tool to rule-out or -in PTE. In the second study, we therefore measured plasma D-dimers using an immunoturbidimetric method (and PT, PTT, TT). None of the dogs showed relevant changes in PT, PTT or TT. The values for plasma D-dimers were 0.17 (0.12-0.35)

µg/ml at T0, 0.37 (0.26-1.21) µg/ml at T1, and 0.50 (0.26-2.37) µg/ml at T2. Determination of D-dimers by immunoturbidometry was neither very sensitive nor specific to detect PTE.

Finally, it has long been described that thoracic radiographs are neither sensitive nor specific to detect PTE. This view has not changed as of today. It is, indeed, very interesting to not that some dogs with most severe obstructive pulmonary vascular disease, as documented by severe pulmonary hypertension, show very unremarkable thoracic radiographs, whereas other dogs with most severe pulmonary changes on thoracic radiographs, induced by vasculitis (with potential or expected PTE), may not show much evidence of pulmonary vascular obstruction as documented by lack of clinically relevant pulmonary hypertension. Thus, even though thoracic radiographs are an important tool to recognize pulmonary (vascular) disease, it is the combination of findings, and in many cases the discrepancy between radiographic (mild) and ultrasonographic (severe) changes that should trigger the suspicion of PTE.

In summary, PTE may be difficult to diagnose using non-invasive and broadly available examination techniques. As indicated above, probably the most important diagnostic clue to detect PTE is a high index of suspicion.

References

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